Iran . J . Immunol
ISSN 1735-1383

Iran. J. Immunol. December 2008, 5 (4), 226-228

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Article Type: LETTER TO THE EDITOR

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A New Paradigm in Biology – The Effect of Localization of a Protein on its Antigenicity

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LETTER

Here, we will discuss the importance of the subcellular localization of proteins (intracellular vs. extracellular) for their antigenicity.
To this end, we will discuss the aberrations in protein trafficking and transport —as well as cellular damage, with regard to cell death and necrosis— that can lead to mixing of compartments that normally are separated in a healthy organism. Thus, we introduce a new hypothesis in biology, wherein the localization of a protein plays a causal role in its antigenicity. A change in the intracellular or extracellular localization can cause an immune reaction, which, if protein transport dysfunction or cell death is continually present over a longer time-period, it will lead to the development of an autoimmune disease.
According to our hypothesis, no defect is necessary within the immune system when an autoimmune disease appears. Aspects of the pathogenetic principle presented here have already been described (1).
1. The Basic Hypothesis. Our basic hypothesis creates a new paradigm, in which the antigen spectrum is separated into intracellular and extracellular antigens. The immune system is also divided into two components— one that copes with intracellular antigens, and another that handles extracellular antigens.
There is a subtype of T-lymphocytes, CD8 T-lymphocytes, that are responsible for the recognition of intracellular antigens— more precisely, cytoplasmic antigens— and a second subtype that is responsible for the recognition of extracellular antigens, CD4 T-lymphocytes.
The underlying principle is a separation of the antigen spectrum that is recognized by CD4 and CD8 T-cell receptors (TCRs). While the CD4 TCR repertoire is responsible for the recognition of extracellular antigens, the CD8 TCR recognizes intracellular antigens.

Keywords: Antigen Presentation, Autoimmune Disease, Autoimmunity, Immune System

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2. The Recognition Process. The law of mass-action applies to the binding of ligands at TCR's:
MHC P + T → [MHC P T] with K = [MHC P T]/ ([MHC P]· [T], where:
MHC P = peptide fragment P bound to MHC-I or II, and T = CD8 or CD4, TCR's.
Thus, the presence of specific T-cells and the presentation of reactive peptides in suitable concentration ratios is sufficient to induce an immune reaction.
If a binding takes place, an intracellular signal transduction cascade within the T-lymphocytes is initiated and propagated, resulting in the subsequent activation and proliferation of these T-cells.
3. Maturation of T-Lymphocytes and Their Specificity. T-lymphocytes undergo a maturation process such that autoreactive T-lymphocytes are eliminated very early during an individual's development.
In an adult, no autoreactivity implies that CD8 T-lymphocytes do not recognize *physiological intracellular proteins* and that CD4 T-lymphocytes do not react against *physiological extracellular proteins*.
Conversely, CD4 T-lymphocytes can in principle still react with intracellular proteins, and CD8 T-lymphocytes can still react with epitopes of extracellular proteins. These events can occur if an intracellular protein suddenly becomes extracellular or vice versa. Thereby, all of these reactions are physiological, except the incorrect protein localization.
4. Errors and Diseases. According to this theory, an autoimmune disease develops when:
(1) an intracellular protein accumulates in the extracellular space,
(2) an extracellular protein accumulates in the intracellular or cytosolic space,
or
(3) the barrier between intra- and extracellular proteins is defective.
Therefore intracellular proteins can accumulate extracellularly through non-apoptotic cell death or through clearance defects. On the other hand extracellular proteins can accumulate intracellularly through protein-trafficking misdirection or through mutations.
Barriers between intracellular and extracellular spaces include the cell membranes as well as the basement membranes (BM) and laminae propriae. Therefore, defects in protein transport will directly lead to activation of the immune system.
Insulin seems to be the major autoantigen in diabetes mellitus type I, as has been described by several groups (2-4). Also strong, sustained overexpression of insulin has been found to be associated with this disease (5). Furthermore several mutations within the insulin-gene have been found to be associated with neonatal diabetes mellitus type I (6,7).
Through the phenomenon of apoptosis, the cell is trying to minimize the amount of intracellular substances released during cell death. So in cases of apoptosis defects, impaired phagocytosis and other cellular clearance deficiencies, autoimmune diseases such as systemic lupus erythematosus should result. This has already been confirmed experimentally (8,9).
5. Physiology. After ubiquitinization, intracellular cytosolic proteins are degraded by proteosomes. The resulting peptides are transported by TAP-transporters (**t**ransporters **a**ssociated with **a**ntigen **p**resentation) into the endoplasmic reticulum (ER) and are directly transferred to MHC-I molecules. In contrast, extracellular proteins are phagocytosed and taken up into vacuoles. In these vacuoles, the consumed proteins are degraded into peptides, after which they are loaded onto MHC-II molecules, a process that requires a low pH.
Although MHC-II molecules are also present in ER, they are initially protected from peptides by the invariant chain. Only after the fusion of MHC-II-containing vesicles

with a lysosome in which extracellular proteins are degraded the MHC-II molecules can be loaded.
Finally, both MHC molecules are presented with their peptide fragments at the cell surface. Here, the MHC-I molecule interacts with CD8 T-lymphocytes, while the MHC-II molecule reacts with the TCR of CD4 cells. This separation is called "MHC restriction." Thus, because the peptides presented by MHC-I and II are distinguished by their intra- and extracellular origin, the antigen spectra of CD4 and CD8 TCRs are also separated.
6. Cross-Presentation. An experimentally well known phenomenon is cross-presentation in which a CD4-stimulus is known to lead to a CD4 and CD8 activation and a CD8-stimulus is known to result in a combined T-cell activation (10-12).
This phenomenon of cross-presentation thereby considers the "output" of the immune system: an MHC-I stimulus leads to a combined proliferation of CD4 and CD8 T-cells. Also, a MHC-II stimulus leads to a combined proliferation of CD4 and CD8 T-cells. In contrast, the hypothesis described here is concerned with the "input": intracellular epitopes lead to an MHC-II activation if released and extracellular epitopes lead to an MHC-I activation if accumulated intracellularly.
Epithelial cells in healthy humans and healthy cats were shown to be devoid of MCH-II molecules beyond the basement membranes, while this is not true in cats exhibiting an inflammatory bowel disease (13). Thereby, this deficiency will sufficiently suppress a CD4-mediated immune reaction. Moreover due to a separation by basement membrane, the remaining cells and the proteins would not leak into systemic circulation.

ACKNOWLEDGEMENTS

No conflict of interest is declared.

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